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the present specification at page 5, lines 14-16. Claim 29 is supported by the present specification at page 6, lines 14-16. Claim 30 is supported by the present specification at page 6, lines 4-5. Claim 31 is supported by the present specification at page 8, line 4. Claims 32-34 are supported by the specification at page 6, lines 20-21.

**Applicants' invention**

The invention is drawn to a method of inhibiting telomerase activity using a specific catechin concentration. Telomerase is much more highly expressed in cancer cells. Consequently, inhibition of telomerase results in a specific inhibition of cancer cells.

Figure 4 as a result of in vitro Example 4 clearly shows that telomerase of cells was effectively inhibited by contacting the cells with an EGCG solution including 15  $\mu$ M of EGCG. The present inventors have unexpectedly found that even this low concentration of EGCG is effective to inhibit the telomerase activity of the cells.

The use of such low concentrations of catechin in cancer treatment is advantageous. High concentrations of catechins, for example EGCG, may inhibit the action of various molecules and may induce a cytotoxic condition. The cellular targets at high concentration of catechins such as EGCG are not limited to cancer cells. On the other hand, telomerase is active in 80-90% of cancer cells but telomerase activity is not observed in non-cancer cells. This makes telomerase an ideal target for selective attack of cancer cells. Thus, the low catechin concentration of the present invention is very effective in attacking cancer cells expressing telomerase, but not non-cancer cells without detectable telomerase expression. The result is an effective strategy to combat cancer with low side effects. The utility of such a low concentration of catechin in treating cancer cells was first discovered by the present inventors and is set forth in the presently claimed invention.

**Rejection under 35 U.S.C. § 112, second paragraph**

Claims 11 and 17-25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This ground of rejection is believed to be moot in view of Applicants' cancellation of previous claims except for the Examiner's point under section C on page 3 of Paper No. 25. On this point, Applicants respond that based upon the evidence of Figure 4, the skilled art worker

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would understand that inhibition of the telomerase activity of the cells may be either in vivo or in vitro.

Applicants respectfully submit that all claims now meet the requirements of 35 U.S.C. § 112, second paragraph.

**Rejection under 35 U.S.C. § 112, first paragraph**

Claims 11 and 17-25 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) has possession of the claimed invention at the time that the application was filed.

This ground of rejection is believed to be moot with regards to the Examiner's first point set forth in the last paragraph of page 4 of Paper No. 25. Regarding the Examiner's second point, Applicants believe that the rejection is based upon the Examiner's misunderstanding of the description set forth in the present specification. As is clear from the results of Example 4, 15  $\mu\text{M}$  is the concentration of the catechin which is contacting the cells. This is not the same as the dosage. Applicants would like to particularly note and emphasize that the concentration is defined in the present specification but not the dosage.

It is clear from the specification (e.g. Example 4) that telomerase activity of cells can be inhibited by contacting the cells with a solution 15  $\mu\text{M}$  catechin concentration, whether in vivo or in vitro. The low concentration of 15  $\mu\text{M}$  is clearly supported by the present specification and drawings. The dosage may be selected from the range on page 7 of the specification so as to provide the low concentration of 15  $\mu\text{M}$  around the cells.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

**Rejection under 35 U.S.C. § 102/103**

Claim 11 and 17-23 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over JP 910108977.

The Examiner asserts that JP910108977 teaches that catechins obtained from green tea concentrates prevented development of colon cancer at concentrations similar to those disclosed by Applicants.

JP910108977 teaches a composition including polyphenols such as catechins as an active component. Section 0010 discloses that the content of the catechin in the composition is

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preferably from 0.05 to 0.7%. However, this range from 0.05 to 0.7% is the catechin content in the composition, but not the in situ concentration for cells to be treated. Although the catechin content of green tea extract is 93%, it is difficult to estimate the concentration of the resultant catechin solution to be contacted with the cells.

If the composition of JP 910108977 is a solution containing 0.05 to 0.7% of catechin and this solution is directly subjected to contact with cells, the concentration of the catechin contacting the cells is approximately in the range from 1.7 to 24 mM. For example, 0.05% of a liter solution contains 500 mg of catechin. 500 mg of catechin corresponds to  $500 \text{ mg} / 290.3 \text{ (MW)} = 1.7 \text{ mM}$ . This concentration range calculated from the catechin content in JP910108977 is much larger than 15  $\mu\text{M}$ . Consequently, JP 910108977 does not anticipate Applicants' claimed invention.

Likewise, JP 910108977 neither teach nor suggest that a concentration as low as 15  $\mu\text{M}$  as claimed is effective to inhibit telomerase activity in cells having telomerase activity. Consequently, JP 910108977 does not render the presently claimed invention obvious.

The Examiner has compared the dose ranges between the present specification and JP 910108977 and noted that the dosage of JP 910108977 (300 to 600 mg/day) overlaps that provided in the present specification (500-2000 mg/day). However, the important characteristic of the present invention is to provide the low catechin concentration of 15  $\mu\text{M}$  contacting the cells to be treated. The dosage concentration to achieve this level is not the same thing as the actual concentration at the cells. The dosage range of the present specification is an example to keep a low catechin concentration of 15  $\mu\text{M}$ .

JP 910108977 does not recognize the inhibitory activity of catechin on telomerase at low concentrations of 15  $\mu\text{M}$ . Consequently, the reference does not provide a motivation to keep the catechin concentration at 15  $\mu\text{M}$  and does not provide a reasonable expectation of success in achieving the advantages of the claimed invention discussed above, namely, effective attack of cancer cells expressing telomerase, but not non-cancer cells without detectable telomerase expression. As discussed above, this results in a cancer treatment with low side effects.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of this ground of rejection is respectfully requested.

Claim 11 and 17-23 are rejected under 35 U.S.C. § 103(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Fujiki et al. or Liao, et al.

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The Examiner asserts that the cited references teach green tea as a cancer preventive and that the presently claimed invention is anticipated under principles of inherency.

Applicants respond that the low catechin concentration of 15  $\mu\text{M}$  has been first found by the present inventors as a result of their investigation of various compounds for inhibition of telomerase. Although the cancer preventive effect of green tea is disclosed by the references, the references do not teach contacting cells with a low catechin concentration of 15  $\mu\text{M}$ . As the application of this concentration of catechins to cells is not taught by either of the cited references, neither reference anticipates the claimed invention. The Examiner has not provided any evidence that drinking green tea will provide a 15  $\mu\text{M}$  concentration of catechin to cancer cells. Consequently, the references do not inherently anticipate the presently claimed invention.

Additionally, the references neither teach nor suggest the catechin concentration necessary to inhibit the telomerase activity of the cells. Consequently, one of ordinary skill in the art would not be motivated to use a concentration as low as 15  $\mu\text{M}$  to inhibit telomerase activity and also cancer cells.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of this ground of rejection is respectfully requested.

**Rejection under 35 U.S.C. § 103(a)**

Claims 24-25 are rejected under 35 U.S.C. § 103(a) as obvious over JP 910108977 or Fujiki et al. or Liao, et al. alone or in view of Cheng or Huang, et al. or Child.

JP 910108977, Fujiki, et al. and Liao, et al. have been discussed above.

Regarding Cheng et al., this reference discloses a method of treating Condyloma acuminata caused by human papillomavirus, comprising applying to an infected catechin as a main composition in an amount effective for treating condyloma acuminata. Example 1 in col. 3, line 38 describes an ointment which contains 5 to 20% of tea catechin. However, it is unclear what catechin concentration can be provided based on the catechin content of Cheng et al. Thus, Cheng et al. neither teach nor suggest the low catechin concentration of the present invention.

Furthermore, the 15  $\mu\text{M}$  used in the present invention corresponds to 6.87  $\mu\text{g/ml}$ . The ointment of Cheng et al. contains 50,000 to 200,000 of tea catechin. It is expected that the ointment of Cheng et al provides a much higher concentration than the present invention.

Additionally, Cheng et al do not teach or suggest the catechin concentration necessary to inhibit telomerase. Consequently, the reference does not provide a motivation to use a 15  $\mu\text{M}$

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concentration of catechins. Consequently, Cheng et al do not correct the deficiencies of the primary reference.

Regarding Huang et al., this reference discloses that the green tea polyphenol fraction inhibits tumor initiation. However, Huang et al. neither teach nor suggest the catechin concentration necessary to inhibit telomerase. Consequently, the reference does not provide motivation to use a 15  $\mu$ M concentration of catechins. Consequently, Huang et al do not correct the deficiencies of the primary reference.

Regarding Child, this reference teaches the use of catechin for manufacture of a medicament for prophylaxis of connective tissue disorders in humans or animals. The daily dosage provided by this reference is between 1-3 g (page 4, lines 32-35). Child does not teach or suggest a catechin concentration necessary to inhibit telomerase. Consequently, the reference does not provide a motivation to use a 15  $\mu$ M concentration of catechins. Consequently, Child does not correct the deficiencies of the primary reference.

As is well-known, a prima facie case of obviousness requires that three basic criteria be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, and must not be based on Applicants' disclosure. In this case, the references cited failed to teach or suggest all of the claim limitations because none of the cited references teach the low catechin concentration presently claimed for telomerase inhibition applied to cells.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

### **CONCLUSION**

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

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Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: March 12, 2003

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